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Dangerous medications – preventing serious side effects

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Dear Subscriber,

On the following pages you will find four documents:

1) A Patient Handout on the several "dangerous" drugs that have been in the news since the FDA official told Congress about them. This Patient Handout covers *Celebrex*, *Crestor*, and several others.
2) A Patient Handout on JUST the COX-2 inhibitors and naproxen (*Aleve*, *Naprosyn*) for you to use if patients are asking about only these.
3) An FDA Talk Paper on use of COX-2 inhibitors and non-selective NSAIDs.
4) Professional Information for you covering all of these drugs.

You may use your choice of either (or both) of the Patient Handouts to suit your needs. Active subscribers have our permission to reproduce copies of the Patient Handouts for you to hand to your own patients. (Mass reproduction or electronic forwarding or dissemination is not authorized.)

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Patient Handout

"Seven Dangerous Drugs" in the News

There have been a lot of recent news reports about some prescription drugs that may be dangerous. These new reports started when Congress was holding a hearing about the painkiller, *Vioxx,* that was taken off the market.

During a Congressional hearing an FDA staff member raised concerns about the safety of some other drugs. He named several drugs: *Accutane* (isotretinoin), *Arava* (leflunomide), *Bextra* (valdecoxib), *Crestor* (rosuvastatin), *Lotronex* (alosetron), *Meridia* (sibutramine), and *Serevent* (salmeterol).

Since the Congressional hearing there have been new reports about two drugs related to *Vioxx.* The two painkiller drugs are *Celebrex* (celecoxib) and *Bextra* (valdecoxib). Recently, *Bextra* was also withdrawn because of the reported problems.

It is important to remember that millions of patients have taken all of these drugs, and the chance of any serious problem is very small. Here is information on the drugs that have been in the news:

Accutane (isotretinoin)

Many people take *Accutane* for severe acne. It is a very effective medicine. It's well-known that *Accutane* can cause birth defects. The problem is that pregnancies continue to occur in women taking *Accutane* despite strict registration programs and mandatory pregnancy blood tests. Part of the problem is that some people get *Accutane* from a friend or from another country.

Women shouldn't take *Accutane* unless they can take strict precautions to avoid getting pregnant. Women who are sexually active should always use two different forms of effective birth control. They shouldn't allow themselves to become pregnant for at least a month after stopping *Accutane*.

Accutane can also make some patients feel depressed, irritable, or lead to suicidal thoughts. There have been suicides in patients taking *Accutane*. Be certain to tell your physician and/or pharmacist right away if you have feelings of depression or self-harm while taking *Accutane*.

Arava (leflunomide)

Arava is an effective drug for treating severe rheumatoid arthritis. Over the years there have been reports of serious lung or liver problems, but these are rare. Patients on *Arava* should get frequent liver function tests to detect any liver problems that might occur. Patients should also report any symptoms of liver problems such as unusual nausea, abdominal pain, fatigue, dark urine, pale stools, or yellow-looking eyes or skin. If a person has any sign of infection that lasts more than a few days, the patient should see a doctor. The signs of infection to watch for are a fever of or above 100.5 degrees, chills, severe sore throat, ear or nose pain, cough, or colored sputum. These might indicate a lung problem.

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Patient Handout

"Seven Dangerous Drugs" in the News

Bextra (valdecoxib) and *Celebrex* (celecoxib*)*

Bextra and *Celebrex* (celecoxib) are used mainly for arthritis pain, menstrual pain, or other pain. Many experts are concerned that *Bextra* and *Celebrex* can lead to an increased chance of heart problems or stroke. *Bextra* and *Celebrex* are similar to *Vioxx* which was just taken off the market due to these types of problems. As of April 2005, *Bextra* is no longer available because of these problems as well as the severe rash it can cause. For more information on *Bextra's* withdrawal from the market go to:
http://www.fda.gov/medwatch/SAFETY/2005/safety05.htm#Bextra.

The chance of a problem in any one patient is very low, but since the problem seems to be related to cardiovascular disease, it makes sense to try to avoid *Celebrex* in patients who have heart problems.

Patients who have heart trouble and are taking *Celebrex* should talk with their health professional.

People who are not likely to benefit from *Celebrex* may be better off on a regular NSAID (such as *Motrin* or *Advil* or a store's brand product) or acetaminophen (such as *Tylenol* or a store's brand product). Patients should discuss this with their pharmacist, NP, PA, or physician.

For more information on *Celebrex* go to:
http://www.fda.gov/medwatch/SAFETY/2004/safety04.htm#Celebrex
http://www.fda.gov/bbs/topics/news/2004/NEW01144.html
http://www.pfizer.com/are/investors_releases/2004pr/mn_2004_1217.cfm

Just recently, the FDA issued a patient advisory statement on naproxen (*Aleve*, *Naprosyn*) which can be bought over-the-counter. Preliminary information from an Alzheimer's disease study showed some evidence of increased risk of cardiovascular events in patients taking naproxen. The FDA advises that patients should not exceed the recommended dose of 220 mg twice daily for longer than ten days unless a physician directs otherwise.

Crestor (rosuvastatin)

Crestor is one of the statins used to lower cholesterol. The consumer group called Public Citizen says it should be taken off the market because of possible kidney and liver problems. These problems are rare and the risk can be minimized by using lower doses and checking kidney and liver function. Anyone taking *Crestor* or another statin should call their health care professional if they start to get muscle pain or weakness, unusual nausea, abdominal pain, fatigue, dark urine, pain when urinating, pale stools, or yellow-looking eyes or skin.

Lotronex (alosetron)

Lotronex is used for women with Irritable Bowel Syndrome (IBS) who have diarrhea frequently, and have failed to get better on other treatments. Reports have been in the news about serious complications. About 1 woman out of 1,000 who takes *Lotronex* may get complications such as severe constipation. It can also cause ischemic colitis, which is caused by low blood flow to parts of the gut. About 1 woman out of 350 women who takes *Lotronex* over a 6 month period may get this. *Lotronex* should never be used in patients who often have constipation. There are other medications for diarrhea or irritable bowel syndrome that don't have these effects.

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"Seven Dangerous Drugs" in the News

Meridia (sibutramine)

Meridia is modestly effective for weight loss, but it can increase blood pressure and heart rate. There are reports of stroke and heart attack in patients taking *Meridia*, but it's not known if these are caused by the drug. Some obese patients already have high blood pressure or heart disease. Patients taking *Meridia* should check their blood pressure and heart rate at least weekly and report any sustained increases to their physician.

Serevent (salmeterol)

Serevent is used to prevent airway constriction in patients with asthma. It's called a long-acting bronchodilator. It may lead to an increased risk of severe asthma worsening, especially when the medicine is not used appropriately. *Serevent* shouldn't be used for sudden breathing difficulties. A short-acting bronchodilator such as albuterol should be used for sudden breathing problems. Also, *Serevent* should always be used with a drug that controls inflammation, such as an inhaled steroid to control asthma and reduce the risk of flare-ups.

Remember

Every medicine has side effects. Your pharmacist, NP, PA, and physician know the possible side effects of drugs and can carefully weigh the benefit of medicines against their risks. Your health care professional will review possible side effects with you and give you information about how to reduce these risks. Be sure to ask any questions you have when a drug is prescribed or dispensed and while you are taking it. Always follow the medication instructions that your health care professional gives you. Never share medications since this is a very dangerous practice. Be sure to get your medicines from a trusted pharmacist.

If you have any concerns, please feel free to discuss them with the health care professional who gave you this handout.

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Information for Patients Taking *Celebrex or* Naproxen

Celebrex (celecoxib) and naproxen (*Aleve*, *Naprosyn*) are used mainly for pain such as arthritis pain. Many patients also use them for menstrual pain. Many experts are now concerned that *Celebrex* and naproxen can lead to an increased chance of heart problems or stroke. *Celebrex* is similar to *Vioxx* and *Bextra* which were taken off the market due to these types of problems. Naproxen is a regular painkiller like *Motrin* or *Advil.*

The chance of a problem in any one patient is very low. It is important to remember that many millions of people have used these medicines and many are still using them. Researchers continuously conduct studies to learn more about the drugs. Recently, researchers were studying to see if *Celebrex* was useful to prevent colon cancer. During the course of the study researchers noticed that there was an increase in heart problems in the people who were taking *Celebrex.* These studies usually run for years and involve many patients. In this case it requires statistical calculations to determine that there was an increase in heart problems in the patients taking *Celebrex.* Just recently, the FDA issued a patient advisory statement on naproxen (*Aleve, Naprosyn*) which can be bought over-the-counter. Preliminary information from an Alzheimer's disease study showed some evidence of increased risk of cardiovascular events in patients taking naproxen. Any individual patient who has taken *Celebrex* or naproxen should not become overly concerned.

Since the problem seems to be related to cardiovascular disease, it makes sense to try to avoid *Celebrex* in patients who have heart problems. Patients who have heart trouble and are taking *Celebrex* or naproxen should talk with their health care professional to see if some other therapy might be better for them.

Bextra, Celebrex, and *Vioxx* are called COX-2 inhibitor drugs. These drugs are actually in the same family of drugs that are called nonsteroidal anti-inflammatory drugs (NSAIDs). One of the problems with some nonsteroidal anti-inflammatory drugs (NSAIDs) is that they can sometimes lead to bleeding in the stomach. It was thought that the COX-2 drugs such as *Bextra, Celebrex,* and *Vioxx* would not lead to as much bleeding in the stomach as the other nonsteroidal anti-inflammatory drugs (NSAIDs). So patients who had ulcers or other chance of bleeding in the stomach or intestinal track often got a drug like *Bextra, Celebrex,* or *Vioxx* instead of the regular nonsteroidal anti-inflammatory drugs (NSAIDs). Pharmaceutical firms encouraged physicians to use these COX-2 drugs for many people. Many people might be better off on an NSAID (such as *Motrin*, *Advil*, or a store's brand product), or acetaminophen (such as *Tylenol* or a store's brand product). The FDA advises that patients should not exceed the recommended dose or duration printed on any over-the-counter medicine bottle unless a physician directs otherwise. Patients should discuss this with their pharmacist, nurse practitioner, physician assistant, and/or physician.

There was a separate concern related to *Bextra*. It could cause severe rash, which in some cases was life-threatening. This reaction was unpredictable, and could happen after short or long periods of use. In April 2005, the FDA asked Pfizer, the manufacturer of *Bextra*, to voluntarily withdraw *Bextra* from the market.

For more information go to:
http://www.fda.gov/bbs/topics/news/2004/NEW01144.html
http://www.pfizer.com/are/investors_releases/2004pr/mn_2004_1217.cfm
http://www.fda.gov/medwatch/SAFETY/2005/safety05.htm#Bextra

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January 2005 ~ Volume 21 ~ Number 210101

FDA Issues Public Health Advisory Recommending Limited Use of Cox-2 Inhibitors

The following excerpts are reprinted from the December 23, 2004 FDA Talk Paper on recommendations for limited use of COX-2 Inhibitors http://www.fda.gov/bbs/topics/ANSWERS/2004/ANS01336.html

Agency Requires Evaluation of Prevention Studies Involving Cox-2 Selective Agents

The Food and Drug Administration (FDA) today issued a Public Health Advisory summarizing the agency's recent recommendations concerning the use of non-steroidal anti-inflammatory drug products (NSAIDs), including those known as COX-2 selective agents. The public health advisory is an interim measure, pending further review of data that continue to be collected.

In addition, FDA today announced that it is requiring evaluation of all prevention studies that involve the COX-2 selective agents *Celebrex* (celecoxib) and *Bextra* (valdecoxib) to ensure that adequate precautions are implemented in the studies and that local Institutional Review Boards re-evaluate them in light of the new evidence that these drugs may increase the risk of heart attack and stroke. A prevention trial is one in which healthy people are given medicine to prevent a disease or condition (such as colon polyps or Alzheimer's disease).

FDA is issuing an advisory because of recently released data from controlled clinical trials showing that the COX-2 selective agents (*Vioxx*, *Celebrex*, and *Bextra*) may be associated with an increased risk of serious cardiovascular events (heart attack and stroke), especially when they are used for long periods of time or in very high risk settings (immediately after heart surgery).

Also, as FDA announced earlier this week, preliminary results from a long-term clinical trial (up to three years) suggest that long-term use of a non-selective NSAID, naproxen (sold as *Aleve*, *Naprosyn*, and other trade name and generic products), may be associated with an increased cardiovascular (CV) risk compared to placebo.

Although the results of these studies are preliminary and conflict with other data from studies of the same drugs, FDA is making the following interim recommendations:

Physicians prescribing *Celebrex* (celecoxib) or *Bextra* (valdecoxib) should consider this emerging information when weighing the benefits against risks for individual patients. Patients who are at a high risk of gastrointestinal (GI) bleeding, have a history of intolerance to non-selective NSAIDs, or are not doing well on non-selective NSAIDs may be appropriate candidates for COX-2 selective agents.

Individual patient risk for cardiovascular events and other risks commonly associated with NSAIDs should be taken into account for each prescribing situation.

Consumers are advised that all over-the-counter (OTC) pain medications, including NSAIDs, should be used in strict accordance with the label directions. If use of an (OTC) NSAID is needed for longer than ten days, a physician should be consulted.

Non-selective NSAIDs are widely used in both over-the-counter (OTC) and prescription settings. As prescription drugs, many are approved for short-term use in the treatment of pain and primary dysmenorrhea (menstrual discomfort), and for longer-term use to treat the signs and symptoms of osteoarthritis and rheumatoid arthritis. FDA has previously posted extensive NSAID medication information at http://www.fda.gov/cder/drug/analgesics/default.htm.

FDA is collecting and will be analyzing all available information from the most recent studies of *Vioxx*, *Celebrex*, *Bextra*, and naproxen, and

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other data for COX-2 selective and nonselective NSAID products to determine whether additional regulatory action is needed. An advisory committee meeting is planned for February 2005, which will provide for a full public discussion of these issues.

FDA urges health care providers and patients to report adverse event information to FDA via the MedWatch program by phone (1-800-FDA-1088), by fax (1-800-FDA-0178), or via the Internet at: http://www.fda.gov/medwatch/index.html.

The Public Health Advisory is available online at: www.fda.gov/cder/drug/advisory/nsaids.htm.

Users of this document are cautioned to use their own professional judgment and consult any other necessary or appropriate sources prior to making clinical judgments based on the content of this document. Our editors have researched the information with input from experts, government agencies, and national organizations. Information and Internet links in this article were current as of the date of publication.

Continue to the next page for more professional information.

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Professional Information

"Dangerous Medications" - Preventing Serious Side Effects

Lead author: Joseph A. Woelfel, Ph.D., FASCP, R.Ph., Assistant Editor

Background

Five drugs were recently cited as posing serious risks as identified by an FDA scientist. On November 18, 2004, Dr. David Graham testified before the US Senate Committee on Finance. Dr. Graham is the Associate Director for Safety, Office of Drug Safety for the Food and Drug Administration. In his presentation made at the hearing on FDA, Merck and *Vioxx*: Putting Patient Safety First, he identified five FDA-approved "dangerous drugs." These include: the diet drug *Meridia*, the cholesterol drug *Crestor*, the acne medication *Accutane*, the anti-inflammatory drug *Bextra*, and the asthma medicine *Serevent*. In his written testimony on *Vioxx*, he included the arthritis drug *Arava*, and the irritable bowel agent, *Lotronex*.[1]

In his testimony, he further stated "I would argue that the FDA as currently configured is incapable of protecting America against another *Vioxx*. We are virtually defenseless." In response to his testimony, Finance Committee Chairman, Senator Chuck Grassley said "that's exactly the opposite of what it should be. The health and safety of the public must be the FDA's first and only concern."[1]

The risks associated with these FDA-approved products that Dr. Graham identified are well known. The larger concern is that there may be system problems in checks and balances for rapid drug approval vs safety assurance.

Minimizing "Dangerous Drug" Effects

Appropriate prescribing, dispensing, administration, and monitoring of medication use are essential for assurance of patient safety.

Accutane (isotretinoin)-related birth defects and suicide or mental problems are well known. In 2002 an isotretinoin risk management program known as the System to Manage *Accutane* Related Teratogenicity (S.M.A.R.T.) was implemented. Currently the FDA is taking action to strengthen the risk minimization action plan (RiskMAP) for *Accutane* and the generic equivalents. Registration of prescribers, pharmacists, and patients will be required before dispensing of isotretinoin. Pregnancy testing before and during isotretinoin is required.[2]

The FDA *Accutane* Medication Guide is essential reading for all patients with each new or refill prescription. Remind them to report any feelings of depression or suicide and for women to use two different forms of birth control.[3]

Arava (leflunomide) for rheumatoid arthritis carries similar pregnancy warnings and contraindications. Women wanting to become pregnant after receiving *Arava* must undergo a process using cholestyramine taken orally for eleven days to clear residual leflunomide from their system. Interstitial lung disease is a serious but rare adverse reaction which was included in the November 2004 product label as a result of post-marketing surveillance data. It can occur any time during treatment. New onset or worsening pulmonary symptoms, such as cough and dyspnea, with or without associated fever, may be a sign of the often fatal problem and warrants follow-up or discontinuation. *Arava* can cause hepatic problems. An unacceptable risk of liver failure was mentioned by Dr. Graham. Monitoring liver function should occur at baseline, at six and 12 weeks after the start of therapy or dose elevation, then every six months.[4] Patients should be reminded to report any signs of liver toxicity such as nausea, abdominal pain, dark urine, or jaundice.

Bextra (valdecoxib) had a new black box warning, added in November 2004. Serious skin rashes can occur anytime but usually occur within the first two weeks of therapy. Advise patients to watch for rashes, lesions, or unusual swelling and discontinue *Bextra* at the first sign of these. They

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should immediately call their health care professional when this occurs. Patients who are recovering from coronary artery bypass graft (CABG) surgery should not receive *Bextra*. In this group of patients *Bextra* is contraindicated due to cardiovascular thromboembolic adverse events. A new bolded warning was added to the label.[6] In recent correspondence to the editor published in the *New England Journal of Medicine*, it was suggested that *Bextra's* use be limited until convincing evidence of cardiovascular safety is shown.[7] On April 7, 2005 the FDA requested that Pfizer withdraw *Bextra* from the market.[15] For more information on *Bextra's* withdrawal go to: http://www.fda.gov/medwatch/SAFETY/2005/safety05.htm#Bextra.

Crestor (rosuvastatin) like other statins can cause rhabdomyolysis or hepatotoxicity. Patients should report any muscle pain or weakness as well as any signs of liver problems such as yellow skin or sclera. The consumer advocacy group, Public Citizen, has admonished *Crestor* for causing kidney damage and rhabdomyolysis. Kidney disease can increase the incidence of rhabdomyolysis and requires dosage adjustment. For patients with severe renal impairment (CL_{cr} <30 mL/min/1.73m2) who are not on hemodialysis, a starting dose of 5 mg once daily is recommended and should not exceed 10 mg once daily. Doses above 10 mg should not be administered to patients taking gemfibrozil (*Lopid*). Initiation of therapy at a dose of 5 mg once daily should be considered for all Asian patients. Lower starting doses are also recommended for the elderly and patients with untreated hypothyroidism.[8]

Lotronex (alosetron) for irritable bowel syndrome lasting over six months in women was withdrawn from the market and then re-introduced in 2002 through a supplemental new drug application process. The new label with prescribing restrictions, black box warning, and a *Lotronex* Risk Management Program reflected the serious adverse events with its use. The incidence of serious complications of constipation in women was approximately 1 per 1,000 patients as shown in clinical trials. The incidence of ischemic colitis was 3 per 1,000 women over a 6 month period.[9] Remind women receiving *Lotronex* to immediately report any constipation, abdominal discomfort, or intestinal bleeding.

Meridia (sibutramine) for weight loss can increase blood pressure and also heart rate. Obese patients may already present with underlying heart and vascular problems so caution in prescribing is essential. *Meridia* is another product under scrutiny from Public Citizen because of these potentially dangerous side effects.[10] Tell patients to check their blood pressure and heart rate regularly, at least weekly, and report any abnormal increases. Emphasize healthy lifestyle changes.

Serevent (salmeterol) received a black box warning label in 2003 concerning the rare but significant risk of asthma-related death shown in the Salmeterol Multi-center Asthma Research Trial (SMART). The risk was greater in African American asthma patients.[11] Life-threatening asthma exacerbation can be reduced by use of an inhaled corticosteroid as recommended in the National Asthma Education and Prevention Program (NAEPP) guidelines.[12] Patients should also receive a short-acting bronchodilator for "as needed" bronchospasm use.

Celebrex (celecoxib). On December 17, 2004, Pfizer issued a news release that in the Adenoma Prevention with Celecoxib (APC) trial, patients taking 400 mg and 800 mg of *Celebrex* daily, had an approximately 2.5 fold increase in major fatal or non-fatal cardiovascular events compared with placebo. As a result of this finding the APC colon cancer prevention trial was stopped. Though higher-than-recommended doses were used in the trial, these findings further raise safety concerns.[13] For more information go to:
http://www.fda.gov/medwatch/SAFETY/2004/safety04.htm#Celebrex
http://www.fda.gov/bbs/topics/news/2004/NEW01144.html
http://www.pfizer.com/are/investors_releases/2004pr/mn_2004_1217.cfm

On December 20, 2004, the FDA issued a patient advisory statement on naproxen (*Aleve*, *Naprosyn*). Preliminary information from an Alzheimer's disease study showed some evidence of increased risk of cardiovascular events in patients taking naproxen. The FDA advises that patients should not exceed the recommended dose of 220 mg twice daily for longer than ten days unless a physician directs otherwise.[14]

On April 7, 2005 the FDA announced that manufacturers of all marketed prescription NSAIDs, including *Celebrex* revise the labeling

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for their products to include a boxed warning and a Medication Guide. The boxed warning highlights the potential for increased risk of cardiovascular events and the potentially life-threatening gastrointestinal bleeding associated with their use. A Medication Guide must accompany every prescription NSAID at the time of dispensing to better inform patients about these risks. The FDA asked manufacturers of non-prescription (OTC) NSAIDs to revise their labeling to include more specific information about the potential risks and provide information to assist consumers in the safe use of the drug.[15]

Active involvement by patients in managing their medication and health with health care professionals' reassuring guidance will minimize the dangerous effects of these drugs.

Users of this document are cautioned to use their own professional judgment and consult any other necessary or appropriate sources prior to making clinical judgments based on the content of this document. Our editors have researched the information with input from experts, government agencies, and national organizations. Information and Internet links in this article were current as of the date of publication.

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